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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,353	08/31/2001	Timothy Hla	UCT-0012-P	2675

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,353	HLA ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 9-26* is/are pending in the application.

4a) Of the above claim(s) *21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDD

DETAILED ACTION

Newly submitted claims 21-26 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are drawn to a method that uses different components and utilizes different method steps where the steps produce different results than that of the elected and examined invention. The instantly claimed method is drawn to method of treating disease with specified inhibitors and the invention of the newly added claims is a method of screening for inhibitors. The classification of claims 21-26 would also be different since the invention could be classified in class 435/4 or 6 or 7.1, for example, while the instantly examined invention is classified in class 514.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21-26 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

Applicant has amended the claims to recite "wherein the antagonist inhibits phosphorylation of T236 of the EDG-1 receptor" there was no support found in the priority documents for this specific class of antagonists. The claims of the instant application are granted a priority date of the filing of the instant application.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 9, and 13-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Durden [US 6,777,439].

Durden et al disclose a method for inhibiting tumor induced angiogenesis via the administration of a PI-3 inhibitor including LY294002 and wortmannin (see claims 1-3, for example).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9, and 13-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. This is a written description rejection.

The instant invention is broadly drawn to a method of inhibiting angiogenesis in vivo (in a whole animal) via the administration of a composition that comprises a pharmaceutically effective amount of an antagonist that inhibits phosphorylation of EDG-1 receptor at T236 and therefore inhibits EDG1 signal transduction. The scope of potential inhibitors remains quite large. For example, the scope of the invention is not limited to inhibitors of EDG-1, but includes antagonists that even indirectly inhibit phosphorylation at T236. This includes inhibitors/antagonists of any component of EDG1 signal transduction that may result in inhibition of such phosphorylation [T236]. The class of potential compounds is so large as to include any small molecule inhibitor (only claims 16 and 20 are limited to small molecules), antibodies, antisense oligonucleotides, peptide inhibitors, etc. The scope of potential inhibitors remains so vast as to include any type of antagonist compound that may antagonize EDG-1 signal transduction via any direct or indirect inhibition of phosphorylation at T236. This means that any component of any EDG-1 signal transduction cascade that results in an inhibition of phosphorylation may be a potential target of the antagonist used in the instantly claimed methods. The scope of potential antagonist compounds is indeed vast. The invention further reads on inhibiting in any animal species, for example.

The instant specification discloses two antisense oligonucleotides targeted to human EDG-1 which inhibits EDG-1 in cell in culture and suggests methods to find other potential antagonist of EDG-1 signal transduction and two small molecule

compounds. The specification as filed does not provide the actual structure of any other EDG-1 signal transduction antagonists that inhibit phosphorylation at T236, for example. If applicant believes that the specification as filed discloses other antagonist structures applicant is invited to point to such disclosure with particularity. The prior art does not provide the description lacking in the instant specification. If applicant believes that the prior art discloses sufficient structures of antagonists known in the prior art to inhibit EDG-1 signal transduction in vivo or which provide for inhibition of unwanted angiogenesis applicant may bring these to the examiners attention and such disclosure will be taken into consideration.

The instant specification fails to provide a description of a sufficient number of species of antagonists that would be representative of the genus embrace for use with the instantly claimed methods. The specification fails to provide a description of any particular structure or structures that would be shared within the genus of antagonist such that one in the art would be apprised of the structure which corresponds to the function of antagonizing EDG-1 signal transduction. The specification has not shown any compounds that have been shown to inhibit angiogenesis in an animal or which has been shown to inhibit EDG-1 signal transduction in vivo. The specification provides insufficient written description to support the genus encompassed by the claim. The specification has shown two small molecules that differ greatly in their structure that inhibit PI-3 in cell in culture but have not shown how these structures might be representative of other structures that would have the properties required to function in the instant methods.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed antagonists, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to

recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the

cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is also directed to University of Rochester v. G.D. Searle & Co., 69USPQ2d (CA FC 2004). One would not know how to make the claimed substance other than by trial and error process." "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. . . '[t]he claimed method depends upon finding a compound that's electively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.

Applicant's arguments filed 6/24/05 have been fully considered but they are not persuasive.

Applicant argues that the claims have been narrowed and that the specification provides methods that can be used to screen for potential inhibitors. It is noted that the scope of inhibitors contemplated in the instant invention is still indeed broad as discussed above in the rejection. The providing of methods of screening for compound does not substitute for a disclosure of the compounds themselves. As applicant has admitted the structures of the compounds is highly variant . . Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The instant specification has not provided an adequate number of compounds or provided a core structure such that one in the art would know the structures of the class of compounds contemplated for use in the instant methods.

Claims 1, and 9-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is broadly drawn to a method of inhibiting angiogenesis in vivo and methods of treating disease via inhibiting angiogenesis via the administration of antagonists of EDG-1 signal transduction that inhibit phosphorylation at T236. As was

described above, the scope of inhibitors is vast. The disclosure of specific potential inhibitors is minimal. For example the specification discloses two antisense oligonucleotides which were shown to inhibit EDG-1 in cells in culture. The specification fails to provide any working examples that show of would show by correlation the inhibition of angiogenesis in vivo or the treatment of disease via an EDG-1 antagonist.

It is noted that the art of biotechnology is an unpredictable art and that the exemplified antisense oligonucleotides of the instant specification are part of an unpredictable art of nucleic acid therapy. It is noted that the claims are so broad to read on any type of antagonist but the following will demonstrate that even a narrow range of what is contemplated is unpredictable and not enabled.

The specification fails to provide any specific guidance for antisense based therapy other than providing two potential oligonucleotides that might be tested where there is not specific guidance for targeting or delivery in an in vivo and/or therapeutic setting. Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem,

and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Branch [TIBS Vol. 23, February 1998 and cited by applicant on form 1449 filed 3/21/02] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of

a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

One in the art would be required to perform an undue quantity of trial and error experimentation to determine potential antagonists from the vast range contemplated and then to further determine how to use such compounds in a method of treatment where it has been demonstrated that at least for antisense oligonucleotides one in the art requires specific guidance on methods or targeting and delivery, for example.

The type of experimentation required to practice the invention more broadly than it is exemplified is a factor in the enablement analysis, but is not dispositive. In this case, the more or less standard nature of each type of experiment to find potential antagonists required to expand the scope of the enabled invention is outweighed by the

sheer quantity of experimentation required to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which the experimentation should proceed.

Applicant's arguments filed 6/24/05 have been fully considered but they are not persuasive.

Applicant asserts that the claimed invention is now limited to non-antisense compounds. It is noted that only claims 16 and 20 are limited to small molecules and the remainder of the claims are still so broad as to read on any inhibitor type so long as the inhibitor causes inhibition of phosphorylation at T236. The invention therefore reads on antisense targted to Akt or PI-3, for example and the antisense grounds are not moot.

Applicant also asserts that method were known for screening for inhibitors, but is is pointed out, as was done in the previous Official Action, that "The type of experimentation required to practice the invention more broadly than it is exemplified is a factor in the enablement analysis, but is not dispositive. In this case, the more or less standard nature of each type of experiment to find potential antagonists required to expand the scope of the enabled invention is outweighed by the sheer quantity of experimentation required to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which the experimentation should proceed."

This point has not been addressed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635

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